

RESEARCH ARTICLE

Tris-isocyanide copper(I) complex enabling copper azide-alkyne cycloaddition in neat conditions

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The three-coordinated homoleptic Cu(I) complex with 2,6-dimethylphenyl isocyanide in the coordination sphere was easily synthesized and isolated as tetrafluoroborate salt. The structure of the compound was determined by single-crystal X-ray diffraction. The complex is highly stable, active and selective toward the copper-catalyzed azide-alkyne cycloaddition, working in neat conditions and in the absence of bases at room temperature. Substrate scope was assessed by testing several different alkynes and azides. In most cases the corresponding 1,4-disubstituted-1,2,3-triazoles were isolated in high yields.

KEYWORDS

click reaction, copper(I), CuAAC, isocyanide, trigonal planar

1 | INTRODUCTION

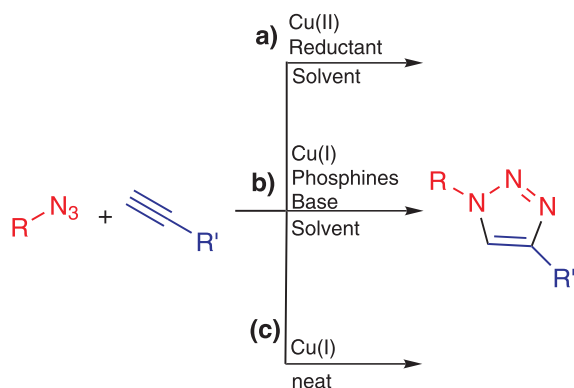
Since 2001, when K. B. Sharpless coined the term “Click Chemistry” referring to a class of high yielding organic reactions based on few simple steps, copper azide-alkyne cycloaddition (CuAAC) emerged as a powerful tool enabling the synthesis of triazoles.^[1–4] The tremendous impact gained by CuAAC mostly relies on the wide use of 1,4-disubstituted-1,2,3-triazoles for a plethora of applications ranging from the synthesis of pharma,^[5–10] polymers,^[11–14] and natural compounds,^[9] to the preparation of ligands for organometallic chemistry and catalyst design.^[15–20]

Despite the massive number of reports present in the literature, the development of new catalytic systems still represents an attracting topic, especially in view of the implementation of the sustainability of processes to be employed also at industrial level.^[4–21]

According to the literature, the most common conditions adopted for copper azide-alkyne cycloaddition involve the use of a Cu(II) precursor, such as CuSO₄·5H₂O or Cu(OAc)₂, generating in situ the active Cu(I) species in the presence of sodium ascorbate as reducing agent and water/alcohol mixture as solvent (Scheme 1a).^[22] The low cost of the reagents and the wide substrate applicability made this catalytic system

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SCHEME 1 (a) General conditions of copper azide-alkyne cycloaddition (CuAAC) in presence of Cu(II) salts; (b) general conditions of CuAAC in presence of Cu(I) catalysts; (c) this work

the most frequently used. On the contrary, the direct addition of Cu(I) metal sources such as copper halides or triflate is less straightforward. In fact, in order to favor the formation of Cu(I) species, bulky organic ligands, mainly phosphines, are added to stabilize the precursors, to prevent the disproportionation and to increase the solubility in organic media (Scheme 1b).^[4] Furthermore, it is widely accessible that the use of a base is beneficial, increasing the turnover of the reaction.^[23]

Hence, the availability of an air-stable Cu(I) complex active in CuAAC allowing to reduce or avoid the use of reductants, bases, solvents, and phosphines is highly attractive in terms of process sustainability. C-donor ligands such as isocyanides and *N*-heterocyclic carbenes (NHC) represent promising and versatile choices to replace phosphines in the coordination sphere of Cu(I) catalytically active complexes.^[24–28] For instance, Liu and Reiser reported the synthesis of a polymeric complex starting from CuCl and 2,4-dimethoxyphenyl isocyanide active toward CuAAC in heterogeneous conditions. Among the advantages, the catalyst could be recovered by filtration and recycled up to five times without loss of activity.^[29] The synthesis of 1,2,3-triazoles in heterogeneous catalytic conditions is of current interest, as demonstrated by the recent reports on catalysts composed by Cu nanoparticles on carbon nanotubes or Cu(II)-coated magnetic core-shell nanoparticles Fe₃O₄@SiO₂ modified by isatoic anhydride.^[30,31] For what concerns Cu(I)-NHC complexes, it is worth noting that NMR and DFT studies revealed that the dissociated NHC ligands are able to deprotonate the coordinated phenylacetylene, favoring the formation of the Cu(I)-acetylide intermediate.^[32]

The interest of our research group toward the synthesis of new triazolyl-containing species prompted us to prepare new and more sustainable Cu(I) organometallic complexes and to test their performances toward

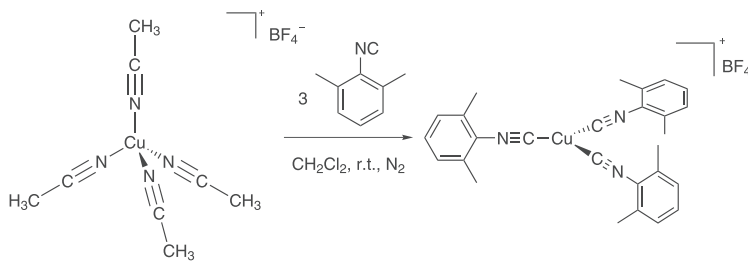
CuAAC.^[16,19,20] The growing attention toward isocyanides as supporting and non-innocent ligands in metal catalysis focused our studies on new Cu(I) isocyanide derivatives.^[33] Thus, in this paper we report the synthesis and structural characterization of a rare example of three-coordinated Cu(I) homogeneous catalyst having formula [Cu(CNXyl)₃][BF₄], where CNXyl is 2,6-dimethylphenyl isocyanide.^[34–37] Remarkable catalytic activity for CuAAC in neat conditions was verified with a wide number of substrates (Scheme 1c).

2 | RESULTS AND DISCUSSION

2.1 | Synthesis and characterization

The complex [Cu(CNXyl)₃][BF₄] was prepared by addition of three equivalents of 2,6-dimethylphenyl isocyanide to the acetonitrile complex [Cu(NCCH₃)₄][BF₄], under mild conditions (see Scheme 2). The elemental analysis supported the proposed formula and conductivity measurements indicated that the complex behaves as 1:1 electrolyte in acetone solutions. IR and ¹H NMR spectra confirmed the disappearance of the coordinated acetonitrile and the coordination of isocyanides. In particular, the band at 2170 cm^{−1} related to the ν_{C≡N} stretching is diagnostic for the coordinated isocyanide. The presence of the counterion is confirmed by a strong band between 1085 and 985 cm^{−1}. As regards the ¹H NMR spectrum, the methyl protons are associated to a singlet at 2.51 ppm (¹³C HSQC 18.74 ppm). The aromatic protons generate one doublet centered at 7.19 ppm (¹³C HSQC 128.23 ppm) related to the *meta*-positions and one triplet at 7.32 ppm (¹³C HSQC 130.33 ppm) for the *para*-position. The *ipso*-carbons in *ortho*-positions of the xylyl ring are associated to a singlet at 135.86 ppm in the ¹³C NMR spectrum, while a weak, slightly broad resonance centered around 149.1 ppm is attributable to the coordinated carbon atoms, shifted at lower frequency with respect to the free ligand (169.5 ppm), as already observed in the literature.^[38] IR and NMR data are in line with those reported for the comparable halide-complex [CuBr(CNXyl)₃].^[39] NMR and IR spectra are provided in the Supporting Information, Figures S1 and S2.

The complex exhibits good thermal stability (decomposition starts around 170°C) and no appreciable oxidation can be detected under air at room temperature. Electrochemical measurements in CH₃CN/LiClO₄ solution showed two irreversible oxidation processes, with peaks around 1.48 and 1.74 V versus Fc⁺/Fc using a glassy carbon electrode and a scan rate of 500 mV/s. A shoulder around −2.07 V and an irreversible peak centered at −2.45 V versus Fc⁺/Fc were observed by

SCHEME 2 Synthesis of $[\text{Cu}(\text{CNXyl})_3][\text{BF}_4]$ 

recording cyclic voltammograms at negative potentials. The reduction processes are not related to the previous oxidation of the compound. The comparison with the cyclic voltammograms obtained for the free isocyanide under the same experimental conditions suggests that the first oxidation process of $[\text{Cu}(\text{CNXyl})_3][\text{BF}_4]$ may be attributed to the coordinated ligands, while the reduction processes probably involve the metal center. Selected cyclic voltammograms are collected in Figure S3, Supporting Information. Similar results were obtained by studying the oxidation of $[\text{Cu}(\text{CNXyl})_3][\text{BF}_4]$ and CNXyl with a gold electrode, despite the fact that the processes occur at lower potentials. In particular, in the case of $[\text{Cu}(\text{CNXyl})_3][\text{BF}_4]$ a first irreversible oxidation process centered around 1.02 V versus Fc^+/Fc is followed by a second oxidation peak at 1.29 V, the latter associated to a reverse peak at 0.59 V. The isocyanide showed under the same experimental condition an irreversible process with maximum at 1.24 V (see the inset of Figure S3, Supporting Information).

2.2 | Crystal structure determination and DFT studies

Crystals of $[\text{Cu}(\text{CNXyl})_3][\text{BF}_4]$ suitable for X-ray determination were collected from dichloromethane/diethyl ether solutions. The compound crystallized in the $P2_1/c$ space group. Crystal data and parameters related to the refinement of the structure are collected in Table S1, Supporting Information. As observable in Figure 1,^[40] the cation consists of a three-coordinated copper(I) compound with three 2,6-dimethylphenyl isocyanide ligands. The Cu atom lies on a non-crystallographic threefold axis and it is bonded to three ligands in a trigonal-planar fashion. This coordination mode was also found in the compound with 2-methoxyisobutylisocyanide (MIBI) ligands $[\text{Cu}(\text{MIBI})_3][\text{BF}_4]$.^[41] The Cu-C bond lengths range from 1.9078(14) to 1.9188(14) Å (see Table 1), and are in good agreement with the value measured for the $[\text{Cu}(\text{MIBI})_3]^+$ cation, equal to 1.917(3) Å. The bond lengths are instead shorter than those found in the tetracoordinated and neutral $[\text{CuBr}(\text{CNXyl})_3]$ complex, comprised between 1.924(2) and 1.946(2) Å.^[39] The

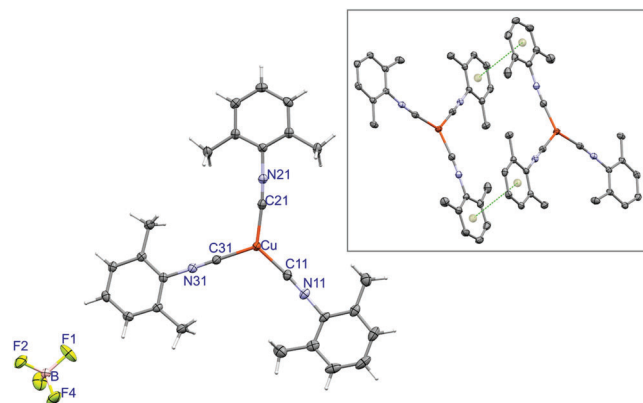


FIGURE 1 Crystal structure of $[\text{Cu}(\text{CNXyl})_3][\text{BF}_4]$. Ellipsoids are drawn at 50% level. Inset: dimeric units formed by π,π -stacking interactions

formally triple $\text{C} \equiv \text{N}$ bond in the isocyanide ligand is 1.15 Å long (see Table 1), slightly more elongated than the value found for $[\text{Cu}(\text{MIBI})_3][\text{BF}_4]$, equal to 1.142(4) Å. On the other hand, because of the sp^2 character of the carbon atoms of the aryl fragment, the formally single N-C bond is slightly shorter (1.40 Å) if compared to the MIBI derivative (1.435(4) Å).^[41] Similar values were found for the $[\text{CuBr}(\text{CNXyl})_3]$ complex.^[39]

As already observed for $[\text{Cu}(\text{MIBI})_3]^+$ and $[\text{Cu}_2(\mu\text{-L})_3]^{2+}$ ($\text{L} = 1,1'$ -diisocyanoferrrocene),^[41,42] $[\text{Cu}(\text{CNXyl})_3]^+$ is not perfectly trigonal, the C-Cu-C angles being 116.12(6), 117.31(6) and 125.96(6)°. The sum, 359.4°, reveals however the planarity of the first coordination sphere and the copper atom is only 0.086(1) Å above the plane defined by the three donor atoms. Nevertheless, the xylyl planes are not coplanar as shows Figure S4 (Supporting Information). The benzene ring planes form dihedral angles of 4.15(2) (between #1 and #2) 8.17(3) (between #2 and #3) and 10.45(2)° (between #1 and #3). Such a behavior could be related to supramolecular interactions (vide infra).

The Cu-C-N arrangements are also not exactly linear, with angles ranging from 171.37(12) to 176.56(13)°. Similar values were found also for the tetracoordinated derivative $[\text{CuBr}(\text{CNXyl})_3]$,^[39] much more bent than the Cu-C-N angles in the tetracoordinated complex

TABLE 1 Selected bond lengths [Å] and angles [°] for [Cu(CNXyl)₃][BF₄]

Cu-C(11)	1.9078(14)	Cu-C(21)	1.9127(14)
Cu-C(31)	1.9188(14)		
C(11)-N(11)	1.1511(18)	N(11)-C(12)	1.4039(17)
C(21)-N(21)	1.1521(18)	N(21)-C(22)	1.4036(16)
C(31)-N(31)	1.1494(18)	N(31)-C(32)	1.3991(17)
C(11)-Cu-C(21)	125.96(6)	C(11)-Cu-C(31)	117.31(6)
C(21)-Cu-C(31)	116.12(6)		
N(11)-C(11)-Cu	171.37(12)	C(11)-N(11)-C(12)	174.63(14)
N(21)-C(21)-Cu	174.73(12)	C(21)-N(21)-C(22)	175.68(13)
N(31)-C(31)-Cu	176.56(13)	C(31)-N(31)-C(32)	178.86(14)

[Cu₂(ox)₂(CNXyl)₄] and in other isocyanide derivatives such as [Cu(CN^tBu)₄]⁺ or the above mentioned [Cu(MIBI)₃]⁺ cation.^[41,43,44]

The presence of the tetrafluoroborate anion allows the formation of several non-classical C-H...F bonds that probably maintain the supramolecular network, since three of the four fluorine atoms are involved. The parameters are set out in Table S2, Supporting Information (see also Figure S5, Supporting Information). Other secondary bonds can be found in the crystal structure. Noteworthy is the π,π -stacking interaction between two xylyl moieties. Such an interaction, shown in the inset of Figure 1, is double and generates dimeric units. The distance between centroids is 3.7172(8) Å and the dihedral angle between planes is 4.14(7)°, so one of the centroids is at only 3.4409(5) Å from the other plane, but the ring is slipped of 1.601 Å with symmetry operation 1-x, 1-y, 1-z. The third xylyl ring is implicated in a stair-like or zig-zag growing along the *c* axis due to an interaction between the π cloud and the metal of a neighbor complex situated at 3.41 Å with symmetry operation *x*, 3/2-*y*, *z*-1/2, as shows Figure S6 (Supporting Information). The shorter Cu-Cu distance found in the compound is 7.431 Å, supported by this interaction. The unit cell contents are set out in Figure S7 (Supporting Information).

The structure of the molecule in a low polar solvent ($\epsilon = 3.0$) was simulated by means of C-PCM/DFT calculations. The central {CuC₃} fragment is roughly superimposable to that determined by X-ray diffraction, as observable in Figure 2. On the other hand, the lack of the intramolecular interactions previously described causes a rotation of the aryl substituents that are much more perpendicular to the {CuC₃} plane with respect to the X-ray structure. The tetrafluoroborate ion is quite close to Cu(I), being the shorter Cu---F distance 2.290 Å, but the molecule maintains the trigonal planar arrangement, being the Cu(I) only 0.125 Å far from the plane determined by the three coordinated carbon atoms.

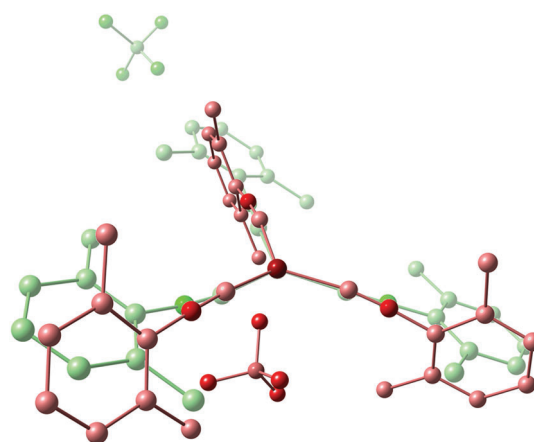


FIGURE 2 Superimposition of the DFT-optimized (red tones) and X-ray (green tones) structures of [Cu(CNXyl)₃][BF₄]. Selected computed bond lengths (Å): Cu-C, 1.963, 1.966, 1.967; Cu---F, 2.290; C $\equiv$ N, 1.164, 1.164, 1.165. Selected computed angles (°): C-Cu-C, 118.2, 120.2, 120.4

Since alkynes were used as solvents in most of the catalytic runs described below, the possible complex formed by [Cu(CNXyl)₃][BF₄] with phenylacetylene was computationally investigated. The DFT-optimized structure of [Cu(CNXyl)₃(HC $\equiv$ CPh)][BF₄] is reported in Figure 3. The reaction [Cu(CNXyl)₃][BF₄] + HC $\equiv$ CPh $\rightarrow$ [Cu(CNXyl)₃(HC $\equiv$ CPh)][BF₄] is associated to a negative enthalpy variation equal to -4.6 kcal mol⁻¹ but, because of the reduction of molecularity, the estimated Gibbs energy variation is positive, +6.3 kcal mol⁻¹. Accordingly, no meaningful change in the ¹H, ¹⁹F and ¹¹B chemical shift values was observed by adding one equivalent of phenylacetylene to a CDCl₃ solution of [Cu(CNXyl)₃][BF₄]. The NMR spectra are provided in the supporting information, Figures S8–S10 (Supporting Information). On the other hand, the high concentration of alkyne in the catalytic runs makes possible the formation in solution of the

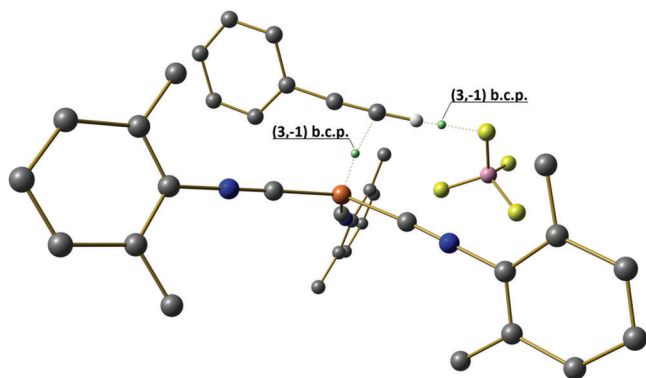


FIGURE 3 DFT-optimized structure of $[\text{Cu}(\text{CNXyl})_3(\text{HC} \equiv \text{CPh})][\text{BF}_4]$. Color map: Cu, orange; N, blue; C, gray; F, yellow; B, pink. Selected (3,-1) b.c.p. are shown in green. Electron density (ρ) and potential energy density (V) values at b.c.p. (a.u.): $\text{Cu} \cdots \text{C}$, $\rho = 0.030$, $V = -0.029$; $\text{H} \cdots \text{F}$, $\rho = 0.026$, $V = -0.021$. Selected computed bond lengths ($\text{\AA}$): $\text{Cu}-\text{C}_{\text{isocyanide}}$, 1.966, 1.983, 1.989; $\text{Cu}-\text{C}_{\text{alkyne}}$, 2.491, 2.652; $\text{H} \cdots \text{F}$, 1.891; $\text{C} \equiv \text{N}$, 1.163, 1.164, 1.165. Selected computed angles ($^\circ$): $\text{C}-\text{Cu}-\text{C}$, 112.0, 115.3, 122.2

complex depicted in Figure 3. AIM^[45] calculations highlighted the presence of two (3,-1) bond critical points (b.c.p.), connecting the phenylacetylene with Cu(I) and the $[\text{BF}_4]^-$ anion. $[\text{Cu}(\text{CNXyl})_3(\text{HC} \equiv \text{CPh})][\text{BF}_4]$ is less planar than the precursor, being the Cu(I) center 0.381 $\text{\AA}$ far from the plane determined by the isocyanide donor atoms. The $\text{H} \cdots \text{F}$ interaction is associated to a slight activation of the phenylacetylene C-H bond, longer in the complex (1.089 $\text{\AA}$) with respect to the free molecule optimized at the same computational level (1.077 $\text{\AA}$). The electron density at (3,-1) C-H b.c.p. decreases upon coordination from 0.279 to 0.274 a.u., and accordingly, the potential energy density is less negative (−0.339 a.u. in the complex, −0.343 a.u. in the free phenylacetylene). The (3,-1) C-H b.c.p. is closer to the hydrogen atom in the complex (0.332 $\text{\AA}$) than in the free molecule (0.368 $\text{\AA}$), suggesting an increase of acidity.

The possible interaction of the tetrafluoroborate anion with coordinated phenylacetylene could explain the broadening of the ^{19}F NMR resonance observed by collecting the spectrum using phenylacetylene as solvent (CDCl_3 as external standard). The comparison of the ^{19}F NMR spectrum with that recorded for a CDCl_3 solution of the complex is shown in Figure S11, Supporting Information. Comparable FWHM values were instead observed for the ^{11}B NMR resonance in phenylacetylene and CDCl_3 (Figure S11, Supporting Information).

Despite that the full comprehension of the mechanism involved in the catalytic activity described below is beyond the scope of this work, the possible behavior of

isocyanide as in situ base was investigated, first supposing the formation of the acetylide-complex $[\text{Cu}(\text{C} \equiv \text{CPh})(\text{CNXyl})_2]$ and $[\text{HCNXYl}][\text{BF}_4]$ after the coordination of phenylacetylene to $[\text{Cu}(\text{CNXyl})_3][\text{BF}_4]$. It was also considered the deprotonation of coordinated $\text{HC} \equiv \text{CPh}$ by free isocyanide, possibly derived from the dissociation from another molecule of complex. The reaction studied in this last case is $[\text{Cu}(\text{HC} \equiv \text{CPh})(\text{CNXyl})_3][\text{BF}_4] + \text{CNXyl} \rightarrow [\text{Cu}(\text{CCPh})(\text{CNXyl})_3] + [\text{HCNXYl}][\text{BF}_4]$. In the first situation the Gibbs energy variation is 37.7 kcal mol^{-1} , while the second reaction is associated to a Gibbs energy variation of 20.5 kcal mol^{-1} . The strongly positive ΔG values rule out the possible behavior of isocyanide as base.

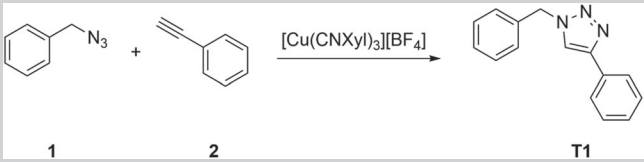
2.3 | Catalytic activity

With the fully characterized complex in hand, we evaluated its catalytic activity toward the copper azide-alkyne cycloaddition. The reaction between benzyl azide (**1**) and phenylacetylene (**2**) to afford 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (**T1**) was initially chosen (see Table 2). Given the easy purification process of **T1**, obtained by simply washing the solid formed during the reaction, optimization was evaluated in terms of isolated yields.

Initially, the conditions generally employed for CuAAC were tested (Table 2, Entry 1).^[16,19,20] **T1** was recovered in 72% isolated yield from a water/methanol 1:1 mixture containing 1 mol% of catalyst after 18 h of reaction time. The selectivity toward the 1,4-disubstituted regioisomer was complete since no traces of 1,5 regioisomer were detected. Similar yield of **T1** was achieved by reducing the reaction time to 6 h (Table 2, Entry 2), allowing us to set this reaction time as starting point for further optimization experiments.

While the use of water alone (Table 2, Entry 3) or methanol (Table 2, Entry 4) still allowed to recover **T1** in good yields, dichloromethane afforded poor yields (Table 2, Entry 5), probably because of the formation of chlorinated Cu-species which slowed down the reaction as previously described in the literature.^[46]

Surprisingly, it was observed that the reaction proceeded faster when no solvent was employed (Table 2, Entry 6). In fact, $[\text{Cu}(\text{CNXyl})_3][\text{BF}_4]$ revealed to be soluble in the reaction mixture obtained by mixing **1** and **2**. In the absence of a solvent, the reaction stopped as the product gradually formed as a white solid. Two hours were sufficient to reach almost quantitative yields of the desired product **T1** (Table 2, Entry 7). For comparison, the $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ /sodium ascorbate catalytic system under the same experimental conditions afforded **T1** in 32% yield.

TABLE 2 Optimization of reaction conditions between benzyl azide (**1**) and phenylacetylene (**2**)


Entry ^a	Solvent (ml)	Time (h)	Yield (%) ^b
1	H ₂ O (1)/MeOH (1)	18	72
2	H ₂ O (1)/MeOH (1)	6	71
3	H ₂ O (1)	6	71
4	MeOH (1)	6	66
5	DCM (1)	6	32
6	/	6	98
7	/	2	96
8 ^c	/	2	55
9 ^c	/	12	93
10 ^c	THF	12	94
11 ^c	Toluene	12	92

^aReaction conditions **1** = 1 mmol; **2** = 1.1 mmol; cat. = 1 mol% T = r.t.^bIsolated yield.^cCat. = 0.1 mol%.

When the catalyst loading was reduced to 0.1 mol% **T1** was obtained in lower yields after 2 h (Table 2, Entry 8), and as at least 12 h were required to reach yield > 90% under these conditions (Table 2, Entry 9). The TON value corresponding to Entry 9 (Table 2) is 930. In order to verify if the reaction was limited by the precipitation of the product, we carried out further catalytic runs considering THF and toluene as solvents (Table 2, Entries 10 and 11). The TON values obtained were 940 (THF) and 920 (toluene), closely comparable to the result obtained in neat conditions.

Despite the fact that the deep investigation of the role of the counter-anion is beyond the scopes of the present work, we tried to add a stoichiometric amount of lithium triflate to the reaction mixture, considering the reaction conditions of Table 2, Entry 6. The yield of **T1** after 2 h was around 56% and only after 12 h 78% was achieved. The addition of lithium triflate revealed therefore to be detrimental for the catalytic activity and it was no further investigated.

Further experiments were carried out in the best reaction conditions, that is, 2-h reaction time, 1 mol% catalyst loading and solvent-free, to verify the robustness of the optimized catalytic system. Consequently, different azides and terminal alkynes were tested to achieve a wide

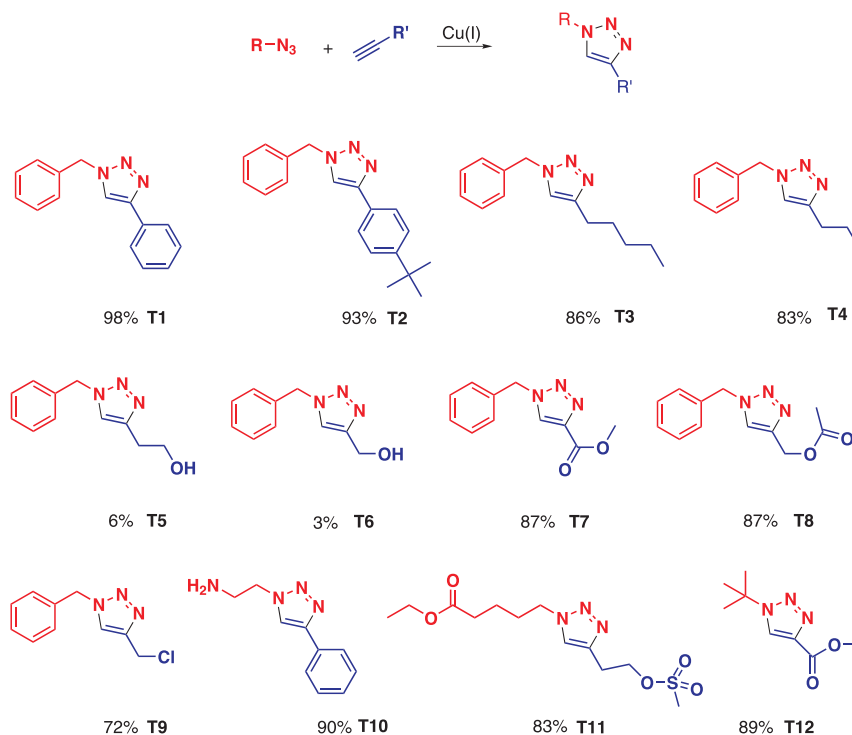
library of 1,4-disubstituted-1,2,3-triazoles as reported in Scheme 3.

The presence of a sterically hindered donating group on phenylacetylene did not slow down the reaction, as 93% of **T2** was isolated. The same performances were maintained in the presence of aliphatic alkynes (**T3** and **T4**).

CuAAC failed when alkynes bearing a terminal hydroxyl groups were tested (**T5** and **T6**) probably due to coordination of the oxygen atom to the metal center. This assumption was verified by protection of the -OH moiety with an acetate group allowing to overcome this drawback, as testified by the high yielding reactions between benzyl azide and methyl propiolate (**T7**) and propargyl acetate (**T8**). Additionally, when propargyl chloride was employed, good yields of the corresponding triazole were obtained (72%, **T9**). A possible explanation is that the hydroxyl-substituted fragments may behave as donor groups toward Cu(I) species in the experimental conditions described, thus inhibiting the catalytic activity of the complex.

Different aliphatic azides were also tested, demonstrating that the reaction proceeded with good tolerance toward different functional groups. As a matter of fact, 2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethan-1-amine (**T10**)

SCHEME 3 Triazoles synthesized using $[\text{Cu}(\text{CNXyl})_3][\text{BF}_4]$ as catalyst and isolated yields. Reaction conditions: azide = 1 mmol; alkyne = 1.1 mmol; cat. = 1 mol%; r.t, 2 h



was recovered in excellent yields, despite the fact that amine moieties could display affinity toward Cu(I) species, as previously verified for hydroxyl functional groups. Finally, the reaction of ethyl 4-azidopentanoate with but-3-ynyl methanesulfonate and *tert*-butyl azide with propargyl acetate afforded the triazoles **T11** and **T12** (see Scheme 3) with yields above 80%. The activity of the catalyst toward most of the substrates is comparable to similar reports making use of Cu(I) catalysts using phosphine ligands and/or amine bases.^[47,48] Characterization data of the isolated triazoles are reported in the supporting information (Table S3, Supporting Information) together with ^1H and ^{13}C $\{^1\text{H}\}$ NMR spectra (Figures S12–S35, Supporting Information).

Finally, the preliminary test carried out with 2-butyne in combination with benzyl azide in neat condition showed no conversion of the substrates; therefore, the catalytic study was not further extended to non-terminal alkynes.

3 | CONCLUSIONS

In this work we described the straightforward synthesis and characterization of a three-coordinated Cu(I) isocyanide complex with trigonal planar geometry, as ascertained by single-crystal X-ray diffraction. The catalytic tests provided clearly indicated noteworthy catalytic activity toward the azide-alkyne cycloaddition, and the most intriguing features are related to the

experimental conditions, such as room temperature and absence of solvents and co-reactants. The catalyst revealed to be tolerant toward a wide variety of substrates and highly selective. NMR experiments suggested the presence of only one species in solution, and the stability observed was corroborated by electrochemical measurements. The one-pot synthesis of the complex, carried out with quite common reactants, makes it a suitable alternative for the catalytic synthesis of triazoles. Finally, the possibility of different functionalizations of isocyanides and the use of different counter-anions open the prospective to develop further catalysts with improved features.

4 | EXPERIMENTAL SECTION

4.1 | Materials and methods

Commercial solvents (Aldrich) were purified following reported procedures in order to be used inside the glove box.^[49] $[\text{Cu}(\text{NCCH}_3)_4][\text{BF}_4]$ was obtained from Cu_2O following a reported synthesis.^[50] Benzyl azide,^[51] 2-azidoethylamine,^[52] *tert*-butyl azide^[53] and ethyl 5-azide valerate^[54] were synthesized following literature procedures. Alkynes were provided by Sigma Aldrich and used as received. The other reagents were Aldrich, TCI or Carlo Erba products used as received.

The synthesis of the complex was carried out under inert atmosphere in a glove box (MBraun Labstar with

MB 10 G gas purifier) filled with N₂ and equipped for inorganic syntheses.

Elemental analyses (C, H, N) were carried out using an Elementar Unicube microanalyzer. Conductivity measurements in acetone were conducted with a Radiometer Copenhagen CDM83 instrument. Melting point measurements were carried out using a modified Falc 360 D apparatus equipped with a video recording device. IR spectra (KBr pellets) were collected in the 4000–400 cm^{−1} range using a PerkinElmer Spectrum One spectrophotometer. Monodimensional nuclear magnetic resonance (NMR) spectra were collected at variable temperature employing Bruker Avance 300 and Avance 400 instruments operating respectively at 300.13 MHz and 400.13 MHz of ¹H resonance. ¹H and ¹³C {¹H} NMR spectra are referred to the partially non-deuterated fraction of the solvent, itself quoted to tetramethylsilane. ¹¹B and ¹⁹F NMR resonances are respectively referred to BF₃·Et₂O and CCl₃F. Cyclic voltammetry measurements were performed using an eDAQ ET014-199 instrument in acetonitrile containing 0.1 M LiClO₄. The solvent was purified following common techniques^[49] and all the measurements were carried out under argon at room temperature. The working electrodes were 1-mm glassy carbon or gold disks, while the auxiliary electrode was Pt-coated titanium rod. The electrodes were provided by eDAQ. Ferrocene was introduced as internal standard and a Pt wire was used as pseudo-reference electrode. ESI-MS analyses were performed using a Finnigan LCQ-Duo ion-trap instrument, operating in positive ion mode (sheath gas N₂, source voltage 4.0 KV, capillary voltage 21 V, capillary temperature 200°C).

4.2 | X-ray structure determination

Crystallographic data were collected at CACTI (Universidade de Vigo) at low temperature using a Bruker D8 Venture with a CMOS Photon 100 detector and Mo-K α radiation ($\lambda = 0.71073$ Å) equipped with a CryoStream 800 system. The software APEX3^[55] was used for collecting frames of data, indexing reflections, and the determination of lattice parameters, SAINT^[55] for integration of intensity of reflections, and SADABS^[55] for scaling and empirical absorption correction. Further crystallographic treatment was performed with the Oscale program.^[56] The structure of the compound was solved by using the SHELXT program^[57] and refined by a full-matrix least squares based on F^2 , SHELXL program.^[58] Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were included in idealized positions and refined with isotropic displacement parameters. Further details

concerning crystal data and structural refinement are given in Table S1, Supporting Information. CCDC 2073393 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. PLATON (version 60720) was used to obtain some geometrical parameters of the cif file.^[59]

4.3 | Computational details

The structures of the compounds were optimized using the range-separated ω B97X DFT functional^[60–62] in combination with Ahlrichs' split-valence polarized basis set (def2-SVP).^[63] The C-PCM implicit solvation model was added to ω B97X calculations, considering $\epsilon = 3.0$.^[64,65] The stationary points were characterized by IR simulations (harmonic approximation), from which zero-point vibrational energies and thermal corrections ($T = 298$ K) were obtained.^[66] Calculations were carried out using Gaussian 09^[67] and the output files were analyzed with Multiwfn, version 3.5.^[68] Cartesian coordinates of the DFT-optimized structures are provided in a separated .xyz file.

4.4 | Synthesis of the complex

The complex was synthesized by slowly adding 2,6-dimethylphenyl isocyanide (125 mg, 0.954 mmol) to a dichloromethane solution (20 mL) containing 100 mg (0.318 mmol) of [Cu(NCCH₃)₄][BF₄]. The solution was stirred overnight, then the solvent was evaporated under reduced pressure. The addition of diethyl ether (about 5 mL) caused the precipitation of a solid that was filtered and dried in vacuo. The complex was crystallized from dichloromethane/diethyl ether solutions. Yield > 75%. Despite the fact that the complex was synthesized under controlled atmosphere, it revealed to be air stable at room temperature.

Characterization of [Cu(CNXyl)₃][BF₄]. Elemental analysis for C₂₈H₂₉BCuF₄N₃ (543.86 g mol^{−1}, %), calcd: C, 60.28, H, 5.24, N, 7.53. Found: C, 60.04, H, 5.26, N, 7.50. M.p.: 170 °C (dec.). Λ_M (acetone, 298 K, ohm^{−1} mol^{−1} cm²): 171. IR (KBr, cm^{−1}): 3080–2990 m/w (aromatic ν_{C-H}), 2955–2850 m/w (ν_{C-H}); 2170 s ($\nu_{C\equiv N}$); 1085–985 s (ν_{BF_4}). ¹H NMR (CDCl₃, 298 K) δ 7.32 (t, $J_{HH} = 7.6$ Hz, 3H, CH), 7.19 (d, $J_{HH} = 7.6$ Hz, 6H, CH), 2.51 (s, 18H, CH₃). ¹³C {¹H} NMR (CDCl₃, 298 K) δ 149.1 (s, br, C_{isocyno}), 135.86 (s, C_{ipso}), 130.33 (s, CH_{para}), 128.23 (s, CH_{meta}), 18.74 (s, CH₃).

4.5 | Catalytic tests

Into a 10-mL vial closed with a screw cap, azide (1.0 mmol), alkyne (1.1 mmol) and complex $[\text{Cu}(\text{CNXyl})_3][\text{BF}_4]$ (0.1–1 mol%) were added in this order. The reaction was then allowed to proceed at room temperature and monitored via TLC. After the total consumption of the starting azide, the solid product was collected by filtration and washed with hexane. When the corresponding triazole was an oil, the reaction mixture was concentrated under vacuum and the residue was finally purified on silica gel (hexane/ethyl acetate). Yields reported are an average of at least two experiments. Characterization data of the synthesized triazoles are collected in the Supporting Information, Table S3.

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AUTHOR CONTRIBUTIONS

Valentina Ferraro: Formal analysis; investigation; validation. **Roberto Sole:** Formal analysis; investigation; validation. **Marco Bortoluzzi:** Conceptualization; formal analysis; funding acquisition; supervision. **Valentina Beghetto:** Conceptualization; formal analysis; funding acquisition; supervision. **Jesús Castro:** Formal analysis; investigation; supervision.

DATA AVAILABILITY STATEMENT

The data that support the finding of this study are available from the corresponding authors upon reasonable request.

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